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Synthesis and odor of optically active 2-*n*-hexyl- and 2-*n*-heptylcyclopentanone and the corresponding δ-lactones

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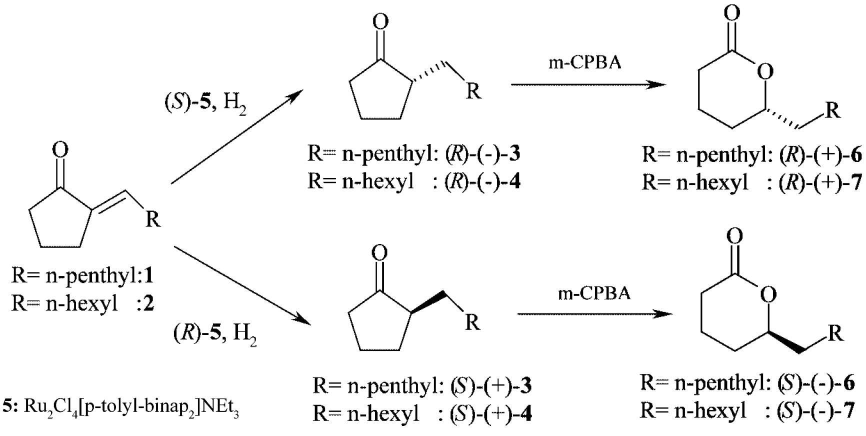
Abstract—Enantiomeric 2-*n*-hexyl- and 2-*n*-heptylcyclopentanones (**3**) and (**4**) have been synthesized by asymmetric hydrogenation of 2-*n*-hexylidene and 2-*n*-heptylidenecyclopentanones (**1**) and (**2**) with Ru_2Cl_4[*p*-*tol*yl-binap]$_2NEt_3$ complexes. The differences in odor qualities between enantiomeric pairs of the ketones **3** and **4** have been found to be small, and the same odor threshold values have been observed between the enantiomeric pairs, although the corresponding δ-undeca- and δ-dodecalactones (**6**) and (**7**), synthesized by Baeyer–Villiger oxidation of the chiral ketones **3** and **4**, showed a fairly large difference in the threshold values between the enantiomeric pairs. © 2002 Published by Elsevier Science Ltd.

Recently, many kinds of olfactory studies on optically active aroma chemicals have been reported.[1] Some of these optically active aroma chemicals show very different odor properties between the enantiomers and the diastereomers. For example, it had been revealed that (+)-methyl epijasmonate, which is a key odorous component of the jasmine flower, showed a different odor and a much lower threshold value than the other three stereoisomers.[2] As related compounds with jasmine odor, racemic 2-*n*-hexyl- and 2-*n*-heptylcyclohexanone are well-known and used for perfume materials. However, the optically active forms have not been synthesized yet, and the odor properties of the enantiomers are unknown.

As for the synthesis of optically active 2-alkylcyclopentanones, Gadkari et al. have reported the synthesis of (*R*)-undecylcyclopentanone by an asymmetric Grignard reaction using (*R*)-2-amino-*n*-butanol. The optical purity of this compound was not described. However, the Baeyer–Villiger oxidation of (*R*)-undecylcyclopentanone yielded (*R*)-5-hexadecanolide in an enantiomeric



Scheme 1.

Keywords: asymmetric hydrogenation; BINAP–Ru(II); Baeyer–Villiger oxidation; 2-*n*-heptyl- and 2-*n*-hexylcyclopentanone; δ-undeca- and δ-dodecalactone; enantiomer; optically active; odor.

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excess of 50%.[3] In another important study, Takaya et al. had reported the highly enantioselective hydrogenations of 2- or 4-alkylidene-γ-butyrolactone and 2-alkylidenecyclopentanone catalyzed by BINAP–Ru(II) complexes. That is, 2-*n*-pentylidenecyclopentanone in CH_2Cl_2 was hydrogenated at 100 atom to afford (*S*)-2-penthylcyclopentanone using a [RuCl{(*R*)-binap}-(benzene)]Cl complex (S/C = 100) in 94% ee and also using a $Ru(OCOCH_3)_2$\{(*R*)-binap\} complex (S/C = 100) in over 98% ee.[4] These situations prompted us to synthesize enantiomeric 2-*n*-hexyl and 2-*n*-heptylcyclopentanones (**3**) and (**4**) to study their odor properties.

We wish to report here the synthesis and odor properties of chiral ketones **3** and **4** and the corresponding δ-lactones **6** and **7**.[5]

Synthetic routes to chiral ketones **3** and **4** and the corresponding δ-lactones **6** and **7** are shown in Scheme 1.

The starting materials (*E*)-2-*n*-hexylidene- and (*E*)-2-*n*-heptylidenecyclopentanones (**1**) and (**2**)[6] were obtained in yields of 76 and 78% by the aldol condensation of cyclopentanone with the corresponding aldehydes (*n*-hexanal and *n*-heptanal) catalyzed by $Ca(OH)_2$ and dehydration with oxalic acid.

As for the asymmetric hydrogenation of **1** and **2**, we have been interested in studying the catalytic activity and the enantioselectivity of the products catalyzed by Ru_2Cl_4[*p*-*tolyl*-binap]$_2NEt_3$ complexes (**5**).[7] As a result, we successfully obtained the chiral ketones **3** and **4** in over 95% ee and with a relative high catalytic activity (S/C = 1000) using the catalytic system of the chiral complexes **5** and MeOH under the mild pressure (30 atm).

A typical procedure is as follows; a degassed mixture of **1** (10 mmol) and the catalyst Ru_2Cl_4[(*S*)-*p*-*tolyl*-binap]$_2NEt_3$ (*S*)-**5** (0.1 mmol) in methanol (12 ml) was stirred under hydrogen pressure (70 atm) in an autoclave (100 ml) for 12 h, at 25°C. After evaporation of the solvent, the mixture was distilled to remove the catalyst. The distillate was purified by silica gel column chromatography to give (*R*)-2-*n*-hexylcyclopentanone (*R*)-**3** (run 1; 89%, 96% ee). (*S*)-2-*n*-Hexylcyclopentanone (*S*)-**3** was also synthesized by using Ru_2Cl_4[(*R*)-*p*-*tolyl*-binap]$_2NEt_3$ (*R*)-**5** in a similar manner. Some representative results are shown in Table 1.

The hydrogenation proceeded under mild conditions; a medium pressure (30–70 atm) and low temperature (25°C). Enantioselectivity, chemoselectivity and catalytic activity were fairly influenced by the solvent. The highest catalytic activities were obtained in MeOH. The

Table 1. Asymmetric hydrogenation of **1** and **2** with chiral Ru_2Cl_4[*p*-*tolyl*-binap]$_2NEt_3$ complexes

Run	Substrate (mmol)	Cat. (S/C)	Solv. (ml)	Temp. (°C)	Press. (atm)	Time (h)	Conv.[a] (%)	Select. (%)	Product		
									Config.[b]	[c]$[\alpha]_D^{25}$	% ee[d]
1	**1** (10)	(*S*)-**5** (100)	MeOH (12)	25	70	12	100	89	(*R*)-**3**	−112.5 (*c* 1.01)	96
2	**1** (10)	(*R*)-**5** (100)	MeOH (12)	25	70	12	100	87	(*S*)-**3**	+112.3 (*c* 1.08)	95
3	**2** (10)	(*S*)-**5** (1000)	*iso*-PrOH (12)	50	30	24	23	51	(*R*)-**4**	–[e]	–[e]
4	**2** (10)	(*S*)-**5** (1000)	EtOH (12)	50	30	24	42	63	(*R*)-**4**	–[e]	–[e]
5	**2** (10)	(*S*)-**5** (1000)	MeOH (12)	50	30	12	100	90	(*R*)-**4**	−101.7 (*c* 1.12)	96
6	**2** (10)	(*S*)-**5** (100)	MeOH (12)	25	70	12	100	87	(*R*)-**4**	−103.3 (*c* 1.00)	97
7	**2** (10)	(*S*)-**5** (100)	Acetone (12)	25	70	24	55	88	(*R*)-**4**	−81.4 (*c* 1.01)	77
8	**2** (10)	(*S*)-**5** (100)	CH_2Cl_2 (12)	25	70	24	94	95	(*R*)-**4**	−102.5 (*c* 0.98)	96
9	**2** (10)	(*S*)-**5** (2000)	MeOH (12)	25	70	8	96	89	(*R*)-**4**	−102.4 (*c* 1.20)	96
10	**2** (10)	(*S*)-**5** (5000)	MeOH (12)	50	30	24	72	83	(*R*)-**4**	−93.9 (*c* 1.15)	88
11	**2** (10)	(*S*)-**5** (10000)	MeOH (12)	75	30	24	70	82	(*R*)-**4**	−94.0 (*c* 1.10)	88
12	**2** (10)	(*R*)-**5** (100)	MeOH (12)	25	70	12	100	88	(*S*)-**4**	+102.9 (*c* 1.04)	97

[a] A conversion was determined by gas chromatography.

[b] Configration was assigned based on that of the lactone synthesized by Baeyer–Villiger oxidation of **3** and **4**.

[c] Solvent; MeOH.

[d] % ee was determined by gas chromatography (Chiraldex G-TA; 0.25 mm I.D.×30 m).

[e] The optical rotation and % ee were not estimated because of the low conversion and low selectivity.

Table 2. Odor properties of the chiral ketones **3** and **4**

Compounds	% ee	Odor properties[a]	Threshold (ppb)[b]
(*R*)-(−)-**3**	96	Powerful diffusive sweet fruity, fatty somewhat jasmone-like floral odor with slightly oily minty citrus note	70
(*S*)-(+)-**3**	95	Powerful diffusive warm jasmine-like floral odor with coconut-like fruity and slightly herbaceous note	70
(*R*)-(−)-**4**	97	Powerful diffusive warm jasmine-like floral odor with somewhat mandalin-like citrus side note and more tenacious than (*S*)-**4**	10
(*S*)-(+)-**4**	97	Heavy, coconut-like oily fruity and jasmine-like floral odor with somewhat herbaceous side note	10

[a] Odor was evaluated on blotters by three perfumers 30 min after neat samples were taken on blotters.

[b] Odor threshold concentrations in aqueous solution were determined by a triangular method similar to that reported by Acree.[2]

Table 3. Optical purity (% ee) and odor properties of the lactones **6** and **7** synthesized by Baeyer–Villiger oxidation[a] of the ketones **3** and **4**

Substrate	% ee	Product	% ee[b]	$[\alpha]_D^{25}/°$ (MeOH)	Odor properties[c] [threshold (ppb)]
(*R*)-**3**	96	(*R*)-**6**	89	+44.9 (*c* 1.02)	Fruity, sweet, creamy [100]
(*S*)-**3**	95	(*S*)-**6**	89	−44.8 (*c* 1.05)	Fruity, sweet, milky [30]
(*R*)-**4**	97	(*R*)-**7**	93	+42.6 (*c* 1.10)	Fruity, sweet, apricot [500]
(*S*)-**4**	97	(*S*)-**7**	92	−42.4 (*c* 1.06)	Fruity, sweet [50]

[a] To the ketone (**3** or **4**; 1 mmol) in CH_2Cl_2 (10 ml) was added *m*-CPBA acid (1.5 mmol) in CH_2Cl_2 (10 ml) at 0°C, then the mixture was stirred at rt for 48 h.

[b] % ee was determined by GC (Chiraldex G-TA; 0.25 mm ID×30 m).

[c] The odor evaluation was done by the same method as for the ketones **3** and **4**.

reaction was completed with S/C = 1000 (run 5), though the conversion was 70% in the case of S/C = 10,000 (run 11). Higher chemoselectivity and enantioselectivities were obtained in MeOH or in CH_2Cl_2 than in acetone, in *iso*-PrOH and in EtOH. The best enantioselectivity of 97% ee was achieved in MeOH with S/C = 100 (run 6).

Table 2 shows odor profiles of the chiral alkylketones **3** and **4** obtained in runs 1, 2, 6 and 12. Odor differences in these enantiomeric pairs were not so large, and they were determined to show a fundamentally jasmine-like floral odor. However, the (*R*)-(−)-forms {(*R*)-(−)-**3** and -**4**} showed a cleaner and more diffusive top-note than the (*S*)-(+)-forms {(*S*)-(+)-**3** and -**4**}.

It is reported that several cyclic compounds show a large difference in the threshold values between enantiomeric pairs, for example, α-damascone[8] shows a 70 times difference in values and nootkatone[9] shows a 750 times difference in values. However, in the present work, the same odor threshold concentrations between the enantiomeric pairs of **3** and **4** have been observed, although five-membered simple cyclic alkylketones **3** and **4** are structurally similar to methyl jasmonate.

Regarding the corresponding enantiomeric δ-lactones, the results of Baeyer–Villiger oxidation of the alkylketones **3** and **4** obtained in runs 1, 2, 6 and 12 using *m*-chloroperbenzoic (*m*-CPBA) acid are shown in Table 3. Baeyer–Villiger oxidation is known to proceed with complete retention of configuration on the asymmetric carbon.[10] However, the optical purities of the products {(*R*)- and (*S*)-**6** and **7**} were a few % lower than those of the substrate {(*R*)- and (*S*)-**3** and -**4**} under the present experimental conditions.

δ-Lactones are widely found in many different kinds of fruits and play very important roles in flavors. A comparison of odor properties of the enantiomers of δ-lactones was reported by Mosandl using the samples prepared by HPLC separation.[11] In the odor evaluation of the present work, it has been identified that the (*S*)-forms have lower threshold values than the corresponding (*R*)-forms, although the corresponding their substrates **3** and **4** show the same values between the enantiomeric pairs (Table 3).

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6. Compounds **1** and **2** (purity; over 99% by GC) were characterized spectroscopically. For **1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, $J=6.9$ Hz), 1.30 (m, 4H), 1.46 (m, 2H), 1.93 (m, 2H), 2.14 (qt, 2H, $J=7.5$, 1.4 Hz), 2.33 (t, 2H, $J=7.8$ Hz), 2.58 (dtt, 2H, $J=2.6$, 1.5, 7.4 Hz), 6.54 (tt, 1H, $J=2.7$, 7.6 Hz). For **2**; ^{1}H NMR: δ 0.88 (t, 3H, $J=6.9$ Hz), 1.30 (m, 6H), 1.45 (m, 2H), 1.93 (m, 2H), 2.14 (qt, 2H, $J=7.5$, 1.4 Hz), 2.33 (t, 2H, $J=7.8$ Hz), 2.58 (dtt, 2H, $J=2.6$, 1.5, 7.5 Hz), 6.55 (tt, 1H, $J=2.7$, 7.6 Hz). MS (m/e): 180 (M^+, 22), 123 (64), 110 (18), 97 (100), 84 (49), 67 (18), 54 (16), 43 (11). The conformations of compounds **1** and **2** were determined to be the (*E*)-form by NOE spectra.
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